

AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING SEPTEMBER 25-26, 2000

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| From mid-June to September 2000 | <p>Protocols:</p> <p>9701-173</p> <p>9709-210</p> <p>9802-233</p> <p>9802-234</p> <p>9808-263</p> <p>9901-280</p> <p>9907-327/328/329</p> <p>9910-346</p> <p>9912-366</p> <p>0002-388</p> <p>0002-391</p> | <p>These thirteen protocols had a total number of 41 new sites/investigators added. Protocol 9802-234 had 15 new sites/investigators. Protocol 9709-210 had 16 new investigators/sites added. The remaining protocols had two or fewer new investigators/sites added.</p> |
| June 6, 2000 (letter date) | <p>9712-225</p> <p>Isola</p> | <p>A Phase I Trial of Autologous and Allogeneic Bone Marrow Transplantation with Genetically Marked Cells for the Treatment of HIV Associated Lymphoid Malignancies.</p> <p>Update: Notification that IND has been withdrawn.</p> |
| June 13, 2000 | <p>9910-350</p> <p>Alberts and Gershenson</p> | <p>A Phase I Dose Escalation Study of Intraperitoneal E1A-Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer</p> <p>Amendments: Eligibility criteria have been broadened to allow enrollment of individuals who have optimal residual disease determined by either an exploratory laparoscopy or laparotomy. Patients must not be refractory to platinum. Inclusion criteria have been amended to modify the time interval from laparoscopy or laparotomy from 4-8 weeks to 1-8 weeks. This change was made to be consistent with the current standard of care.</p> |
| June 20, 2000 | <p>9212-034</p> <p>Crystal</p> | <p>A Phase I Study, in Cystic Fibrosis Patients, of the Safety, Toxicity, and Biological Efficacy of a Single Administration of a Replication Deficient, Recombinant Adenovirus Carrying the cDNA of the Normal Human Cystic Fibrosis Transmembrane Conductance Regulator Gene in the Lung</p> |

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| | | Update: Notification that protocol is closed and IND is inactive. |
| June 20, 2000 | 9904-304 Hurwitz | Pediatric Phase I Study of AdV/RSV-TK Followed by Ganciclovir for Retinoblastoma Amendments: Immunologic studies, six weeks after the last injection, have been added. Patients who would normally be excluded from participation strictly for laboratory abnormalities may be included at investigator's discretion after consultation with the Baylor College of Medicine Cell and Gene Therapy Protocol Review Committee and the FDA. Serious adverse events will be reported to the RAC. |
| June 20, 2000 | 9409-083 Zeitlin and Flotte | A Phase I Study of an Adeno-associated Virus-CFTR Gene Vector in Adult CF Patients with Mild Lung Disease Amendments: Amendments one through nine (submitted to the FDA from July 28, 1995 to July 11, 1997), not previously submitted to OBA, were submitted. (For each amendment, an entire revised clinical protocol was submitted. Major changes for each amendment are as follows: # 1 Decontamination procedures for the home were added. # 2 Toxicity grading criteria were clarified. Blood tests for the vector were added. Time between enrollment of additional individuals in a cohort increased from one to two weeks. # 3 Hospital stay reduced from 18 to seven days. # 4 Hospital stay reduced from seven to four days. Baseline will now be determined over two different outpatient visits. # 5 Individuals with a glycine to aspartic acid change at position 551 are now eligible for the study. # 6 Individuals with a mutation resulting in chain termination at position 1282 are now eligible. Increase in the total number of individuals treated from 12 to 16 and the addition of two cohorts. # 7 Posttreatment studies will now be carried out only until three months, instead of one year. Positive PCR results have not been observed after 90 days. Patients, however, will be followed for one year for safety purposes. # 8 Increased enrollment to 17 patients; one patient did not receive administration to the lung. Therefore study requires an additional patient to complete dosing in all cohorts. # 9 Addition of a ninth cohort and a corresponding increase in the number of patients from 17 to 19. Nasal dose for the additional cohort is increased 10-fold, dose for lung administration is the same as in the eighth cohort. |
| June 22, 2000 | 9903-297 Krance | Intensive Immunosuppression Followed by Rescue with CD34 Selected, T Cell Depleted, Leukopheresis Products in Patients with Multiple Sclerosis Amendments: Eligibility criteria have been amended to indicate, more clearly, that patients are to be off of other investigational therapy for at least one month. In addition, patients who would normally be excluded from participation strictly for laboratory abnormalities may be included at investigator's discretion after consultation with the Baylor College of Medicine Cell and Gene Therapy Protocol Review Committee and the FDA. Male partners should use a condom. |
| June 23, 2000 | 0002-388 | A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 (AD_{GV} VEGF_{121.10}) in |

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| | Rajagopalan <i>et al.</i> | <p>Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication</p> <p>Amendments: Follow-up plasma VEGF levels will be measured at earlier times post vector administration to enhance safety. An “Endpoint Events Committee” has been replaced by an independent Data and Safety Monitoring Board (DSMB) that will review unblinded (if necessary) data as opposed to blinded endpoint events. Events that had been previously defined as those relating to the natural history of the disease--“endpoint events” will now be classified as a subset of adverse events that will be reviewed by the DSMB.</p> <p>At four of the clinical sites, in-depth studies will be performed to determine plasma VEGF and vector levels. In addition, adenoviral cultures will be obtained in throat and urine specimens two weeks postinjection.</p> <p>Finally, at one site a study will be carried out to examine the effect of angiogenesis on muscle metabolism of the lower limbs.</p> |
| June 23, 2000 | 0001-387 Kornowski | <p>A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 12-Week Follow-up, Pilot Study of the Tolerability and Feasibility of Administering AD_{GV} VEGF_{121.10} (CI-1023) Via the Biosense Intramyocardial Injection Device to Patients with Advanced Coronary Artery Disease</p> <p>Amendments: Follow-up plasma VEGF levels will be measured at earlier times post vector administration to enhance safety. Role of the Data and Safety Monitoring Board (DSMB) has been clarified.</p> |
| June 23, 2000 | 9910-346 Stewart <i>et al.</i> | <p>A Phase II, Randomized, Multicenter, 26-Week Study to Assess the Efficacy and Safety of CI-1023 Delivered Through Minimally Invasive Surgery Versus Maximum Medical Treatment in Patients with Severe Angina, Advanced Coronary Artery Disease, and No Options for Revascularization</p> <p>Amendments: Inclusion criteria have been amended at several participating sites to indicate that individuals with Stage III or IV, as opposed to II to IV, coronary artery disease and angina are now the target population for this trial. Change was made to comply with the local ethics committee.</p> <p>At one participating site, a different stress test than the one in the protocol is routinely performed. Therefore, results from the stress test from this one site will not be incorporated in the final analysis of the results from this study.</p> |
| June 27, 2000 | 9706-196 Smith and Dinauer | <p>Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study.</p> <p>Update: Received a copy of the annual report submitted to the FDA. A total of two patients have been enrolled out of five proposed. The two individuals are 8 and 14 months post-infusion and have not experienced any problems that have been determined, by the investigators, to be study-related.</p> |
| | 9910-345 Wilding | June 27, 2000 |
| June 27, 2000 | 9908-336 Smith | <p>Post-Transplant Infusion of Fibronectin-Assisted, Retroviral-Mediated Gene-Marked and Ex Vivo Expanded CD34+ Placental and Umbilical Cord Blood Cells</p> <p>Update: Received additional pre-clinical data, submitted to the FDA, in response to the IND clinical hold. Percentage transduction in nine cord blood samples ranged from 13 to 46%.</p> |

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| June 29, 2000 | 9902-287 Schiller and Carbone | <p>Phase I Pilot Trial of Adenovirus p53 in Bronchioloalveolar Cell Lung Carcinoma (BAC) Administered by Bronchoalveolar Lavage</p> <p>Amendments: Dosing has been changed to indicate that the last 10 patients will be treated at the maximum tolerated dose (MTD) "...to increase the likelihood of detecting serious toxicities." Based upon experience at dose level four (one patient out of five treated experienced a grade 5 toxicity, no other patients experienced a dose limiting toxicity), a MTD of 5×10^{11} pfu has been selected.</p> <p>In addition, adverse event reporting has been clarified to indicate that reports are to also be sent to the Institutional Biosafety Committee.</p> |
| July 5, 2000 | 9510-130 Roskrow <i>et al.</i> | <p>Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin Disease</p> <p>Amendments: Eligibility criteria have been amended to indicate, more clearly, that patients are to be off of other investigational therapy for at least one month. In addition, patients who would normally be excluded from participation strictly for laboratory abnormalities may be included at investigator's discretion after consultation with the Baylor College of Medicine Cell and Gene Therapy Protocol Review Committee and the FDA. Male partners should use a condom.</p> <p>Administration of T lymphocytes will be over 1-10 and not 10-15 minutes as previously indicated.</p> |
| July 5, 2000 | 9510-129 Roskrow <i>et al.</i> | <p>Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes as Therapy for Patients Receiving a Bone Marrow Transplant for Relapsed EBV-Positive Hodgkin Disease</p> <p>Amendments: Eligibility criteria have been amended to indicate, more clearly, that patients are to be off of other investigational therapy for at least one month. In addition, patients who would normally be excluded from participation strictly for laboratory abnormalities may be included at investigator's discretion after consultation with the Baylor College of Medicine Cell and Gene Therapy Protocol Review Committee and the FDA. Male partners should use a condom.</p> <p>Administration of T lymphocytes will be over 1-10 minutes.</p> |
| July 5, 2000 | 9701-175 Lieberman <i>et al.</i> | <p>Gene Therapy for Recurrent Glioblastoma Multiforme: Phase I Trial of Intraparenchymal Adenoviral Vector Delivery of the HSV-TK Gene and Intravenous Administration of Ganciclovir</p> <p>Amendment: Notification that vector dose will now be measured in virus particles.</p> |
| July 6, 2000 | 9804-243 Crystal, Deitcher and Goldman | <p>Phase I Study of Direct Administration of a Replication Deficient Adenovirus vector (Ad_{Gv}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease</p> <p>Update: Trial is completed at one site Cleveland Clinic Foundation. Long-term follow-up has been redefined from five to one year.</p> |
| July 18, 2000 | 9804-243 Crystal <i>et al.</i> | <p>Phase I Study of Direct Administration of a Replication Deficient Adenovirus vector (Ad_{Gv}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease</p> <p>Update: Notification that one participating site, University of Pennsylvania Health System (PI: Dr. Mohler), has completed enrollment. One patient completed the study, whereas a second patient was lost to follow-up.</p> |
| July 25, 2000 | 9701-175 | <p>Gene Therapy for Recurrent Glioblastoma Multiforme: Phase I Trial of Intraparenchymal Adenoviral Vector Delivery of the HSV-TK Gene and</p> |

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| | Lieberman <i>et al.</i> | <p>Intravenous Administration of Ganciclovir</p> <p>Amendments: Women must undergo a pregnancy test prior to enrollment and use contraception, if appropriate, during the trial. Monthly assays for adenoviral shedding will be performed for six months post administration, instead of one year; due to a lack of observed vector shedding.</p> <p>Liver function tests will be performed every other day post-surgery. Due to the potential side effect from ganciclovir.</p> |
| July 25, 2000 | 9908-336 Smith | <p>Post-Transplant Infusion of Fibronectin-Assisted, Retroviral-Mediated Gene-Marked and Ex Vivo Expanded CD34+ Placental and Umbilical Cord Blood Cells</p> <p>Update: Received information submitted to the FDA regarding manufacturing procedures in response to the IND clinical hold.</p> |
| July 26, 2000 | 9912-361 Cassileth <i>et al.</i> | <p>Elicitation of a Cellular Immune Response in Patients with Non-Small Cell Lung Cancer by Immunogenic Tumor Cell Vaccination - A Phase I Study.</p> <p>Amendment: To allow non-HLA A1 or HLA A2 individuals to receive HLA A1 or A2 transfected allogeneic cells.</p> |
| July 27, 2000 | 0005-397 Sanborn | <p>A Feasibility Study of Catheter-Based Administration of a Replication Deficient Adenovirus Vector (Ad_{CU} VEGF.1) to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease</p> <p>Amendments: Changes were made based upon suggestions made by the RAC during its review. A complete copy of the clinical protocol, incorporating these changes, was submitted.</p> <p>To the inclusion criteria:</p> <ol style="list-style-type: none"> 1) Patients must have severe, class III or IV, angina 2) Patients must be treated with maximal therapy for at least two months prior to vector administration. Therapy must have failed to completely control symptoms. 3) Within 12 months of randomization in this trial, patient must have either i) coronary angiographic evidence of stenosis or ii) prior Q wave myocardial infarct 4) Individuals must be able to undergo an exercise tolerance test for at least 90 seconds but not for more than eight minutes 5) Patient must not be, for the foreseeable 12 weeks of randomization, a candidate for i) revascularization by CABG, PTCA, or intravascular stenting; ii) surgical transmyocardial or percutaneous revascularization; or iii) heart transplant 6) Lack of allergy or increased sensitivity to device components. 7) No history of malignancy. <p>Informed consent and protocol were updated to include additional information regarding risks. Language added is the following: "Among the 31 individuals with CAD who received Ad vectors, 5 deaths were reported. These deaths were assessed individually in relation to the Ad vector <i>per se</i> (none were judged as possibly linked). Given that patients enrolled in these CAD trials were relatively ill and at high risk due to their advanced diffuse CAD, these numbers were compared to that of comparable patient populations with severe CAD in other studies, including coronary endarterectomy and laser transmyocardial revascularization. Assessment of these data demonstrate that the mortality in our earlier studies is consistent with that expected for</p> |

this population.”

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| July 28, 2000 | 9911-356 Figlin and Belldgrun | <p>Phase I Bridging Trial of TG4010 as Antigen-Specific Immunotherapy in Patients with MUC-1 Positive Advanced Cancer</p> <p>Amendment and Update: Enrollment has stopped after the first dose level due to the fact that a “sister” protocol being conducted, in Switzerland, has completed enrollment at a higher dose than that planned for this protocol without observation of either grade 3 or 4 toxicities.</p> <p>The sponsor for this study, Transgene, Inc., has provided additional information (this information has also been provided to the FDA and the PI will notify the IBC and IRB) regarding production of the pox virus vector (TG4010). Production lots of this vector contain, in approximately 20-25% of the genomes, a mutation in the transgene. The sponsor notes that the toxicology studies that were performed in support of this vector were done with material that contains this mutation. All patients who have received TG4010 (3 in the US and 10 in Switzerland) are being assessed as to a potential immune response to the altered peptide that is produced due to the one base deletion (which results in a frameshift creating a polypeptide of 169 amino acids).</p> <p>Clinical grade material is being reconstructed by the sponsor.</p> |
| August 7, 2000 | 9412-097 Venook and Warren | <p>Gene Therapy of Primary and Metastatic Malignant Tumors of the Liver Using ACN53 Via Hepatic Artery Infusion: A Phase I Study</p> <p>Update: Received copy of notification to the IRB that trial was placed on clinical hold.</p> |
| August 7, 2000 | 9810-268 and 0001-386 Antonia | <p>Treatment of Patients with Stage IV Renal Cell Carcinoma with B7-1 Gene-Modified Autologous Tumor Cells and Systemic IL-2 and Phase II Study of a B-7.1 Gene Modified Autologous Tumor Cell Vaccine and Systemic IL-2 for Patients with Stage IV Renal Cell Carcinoma</p> <p>Update: Notification, from the Vice President for Research, that these two trials have been placed on clinical hold by the FDA.</p> |
| August 9, 2000 | 9701-175 Lieberman <i>et al.</i> | <p>Gene Therapy for Recurrent Glioblastoma Multiforme: Phase I Trial of Intracranial Adenoviral Vector Delivery of the HSV-TK Gene and Intravenous Administration of Ganciclovir</p> <p>Update: Notification that IRB approved continuation of the study for an additional year.</p> |
| August 10, 2000 | 9802-260 Hersh | <p>Phase I Study of HLA-B7/b2M Plasmid DNA/DMRIE/DOPE Lipid Complex (AlloVectin-7) by Direct Gene Transfer with Concurrent Low-Dose Subcutaneous IL-2 Protein Therapy as an Immunotherapeutic Regimen in Malignant Melanoma.</p> <p>Amendment: Individuals who have received more than one prior chemotherapy/biotherapy are now eligible for enrollment.</p> |
| August 15, 2000 | 9905-319 Brenner | <p>Treatment of High Risk Acute Leukemia with CD40 Ligand and IL-2 Gene Modified Autologous Bone Marrow Fibroblasts and Tumor Cells</p> <p>Amendments: Changes have been made to the background sections of the protocol to include current information. Patients must be willing to use effective birth control during and for three months after completion of the study. In addition, patients who would normally be excluded from participation strictly for laboratory abnormalities may be included at investigator's discretion after consultation with the Baylor College of Medicine Cell and Gene Therapy Protocol Review Committee and the FDA.</p> <p>Informed consent has been amended to state that enrollment in this protocol is not</p> |

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| | | meant to replace standard chemo/radiotherapy. |
| August 15, 2000 | 9510-130 Roskrow <i>et al.</i> | <p>Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin Disease</p> <p>Amendments: Administrative changes have been made.</p> <p>Major change is that gene marking, with the gene encoding neomycin resistance, is now optional. Changes have been made to the protocol to reflect this.</p> |
| August 17, 2000 | 9510-129 Roskrow <i>et al.</i> | <p>Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes as Therapy for Patients Receiving a Bone Marrow Transplant for Relapsed EBV-Positive Hodgkin Disease</p> <p>Amendments: Administrative changes have been made.</p> <p>Major change is that gene marking, with the gene encoding neomycin resistance, is now optional. Changes have been made to the protocol to reflect this.</p> |
| August 24, 2000 | 9804-243 Crystal et al. | <p>Phase I Study of Direct Administration of a Replication Deficient Adenovirus vector (Ad_{Gv}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease</p> <p>Update: Notification that patient enrollment is completed at one site, Univ. of Pittsburgh (PI: Dr. Trachtenberg). Nine patients were enrolled. Six have completed the one year follow-up, two have withdrawn consent, and one patient has been lost to follow-up.</p> |
| August 25, 2000 | 0005-396 Fong | <p>A Phase I Study of the Safety, Tolerability, and Activity of the Intrahepatic Arterial Injection of Escalating Doses of NV1020, a Genetically Modified Herpes Simplex Virus, in Patients with Hepatic Metastases of Colon Carcinoma</p> <p>Amendments: Made in response to the June 2000 RAC review of the trial. Changes include:</p> <ol style="list-style-type: none"> 1) Dividing the protocol into two. One protocol is for the administration of NV1020 and the second is for long-term follow-up, out to one year. Both protocols will be registered as 0005-396. 2) Inclusion criteria clarified to indicate that individuals who have failed first-line combination chemotherapy will be included 3) Individuals who are HSV-1 antibody negative and have documented extrahepatic metastases will not be eligible 4) Immune status (CD4; CD4/CD8) will be determined at baseline. Cytokine response will be determined. 5) Intrahepatic pump will be placed, if feasible, at an earlier time after NV1020 injection to assess circulating virus. <p>In addition, the maximal number of patients has been reduced from 48 to 27.</p> |
| August 25, 2000 | 9503-103 Morgan and Tavel | <p>Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins.</p> <p>Amendment: Clinical protocol has been amended to reflect the fact that the vectors LATRSN and G1Na.40 will no longer be employed in this study.</p> |
| August 28, 2000 | 9905-318 | A Phase II Study of SCH 58500 in Combination with Chemotherapy Alone in |

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| | Venock <i>et al.</i> | <p>Patients with Colorectal Cancer Metastatic to the Liver</p> <p>Update: Notification that the Emory University IRB has approved FDA clinical hold and has approved changes to the informed consent.</p> |
| September 5, 2000 | 9911-358 Sung and Woo | <p>Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12cDNA by Intratumoral Injection in Patients with Metastatic Breast Cancer to the Liver.</p> <p>Amendments: Changes have been made as requested by the FDA. Including a lowering of the dose limiting toxicity, to any grade 3 or greater event and criteria to cease further enrollment to include a grade 2 or greater toxicity in three patients within a dose level.</p> |
| September 5, 2000 | 9911-359 Sung and Woo | <p>Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12cDNA by Intratumoral Injection in Patients with Primary or Metastatic Malignant Tumors in the Liver.</p> <p>Amendments: Changes have been made as requested by the FDA. Including a lowering of the dose limiting toxicity, to any grade 3 or greater event and criteria to cease further enrollment to include a grade 2 or greater toxicity in three patients within a dose level.</p> |
| September 5, 2000 | 0002-389 Sung | <p>Phase I/IB Trial of Combination Adenoviral Vector Delivery of the Human Recombinant Interleukin-2 Gene and the Herpes Simplex Virus Thymidine Kinase Gene by Intratumoral Injection and Followed by Intravenous Ganciclovir in Patients with Hepatic Metastases from Colorectal Cancer.</p> <p>Amendments: Changes have been made as requested by the FDA. Including the lowering of the dose limiting toxicity to any grade 3 or greater event and that the FDA will be notified prior to further enrollment if three or more patients experience a grade 2 event or if two or more patients experience a grade 3 event with a dose level.</p> |